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CARDIAC AND PERIPHERAL EFFECTS OF DOPAMINE
INFUSION IN ENDOTOXIN SHOCK IN THE DOG
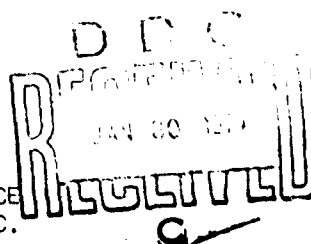
Linda L. Shanbour and Lerner B. Hinshaw

Technical Report No. 12
University of Oklahoma Medical Center THEMIS Contract

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ABSTRACT

The present investigation was designed to evaluate the cardiovascular

effects of dopamine (3-4 Dihydroxyphenylethylamine) in dogs administered

endotoxin. In order to separate peripheral from cardiac effects, a venous

return preparation was used in which cardiac inflow was held constant.

Intra-atrial infusion rates of dopamine between 17 and 34 μg/kg/min caused

increases in venous return and mean systemic arterial pressure. Dopamine

markedly prevented pooling following an LD_{80} of endotoxin until infusion

was stopped. Ten minutes after cessation of dopamine infusion, pooling

rates were not significantly different from those of the untreated, shocked

animals. Dopamine infusion begun ten minutes after endotoxin injection

resulted in tachycardia and decreased left atrial pressure in the presence

of a steady cardiac input and relatively constant systemic vascular

resistance. Right atrial pressure and pulmonary vascular resistance were

maintained above pre-endotoxin values during dopamine infusion, while

portal vein pressure fell and venous return progressively increased. Results

from survival studies in correlation with the above findings suggest

beneficial actions of dopamine on both the left ventricle and peripheral

vasculature in maintaining an adequate circulating blood volume.

Previous studies have clearly demonstrated that the primary drop in arterial pressure following an intravenous injection of endotoxin in dogs is 'ue to a decrease in venous return (10,14). It was further shown that the cause of t..e drop in venous return is hepatosplanchnic pooling, resulting primarily from hepatic venous constriction. Because of the obvious precipitation of severe shock (hypotension) by such a pooling mechanism, any pharmacological agent capable of blocking this action of endotoxin could be considered of major interest in the treatment of shock.

Preliminary clinical studies have suggested that dopamine exerts beneficial effects in patients in various shock states (9). Dopamine (3-4 Dihydroxyphenylethylamine) is reported to have direct actions on the heart (1,4,8,9,11,13). Little, however, is known concerning its action on the peripheral circulation, especially during shock due to endotoxin. Dopamine has shown beneficial cardiac effects in recently published experiments in hemorrhagic shock (3). The effect of dopamine on the peripheral vasculature is apparently highly variable and species dependent. Holtz et al. (6) reported that it is depressor in the guinea pig and rabbit but pressor in the cat and dog. These results were later confirmed by Hornykiewicz (7). Burn and Rand (2) have shown that dopamine is pressor in the spinal cat but depressor in the cat anesthetized with urethane. Large doses appear to elicit a pressor response in the dog (11), while small doses exert a depressor action (4). Ross and Brown (13) studied the effects of dopamine on various vascular beds in the anesthetized cat. They reported vasodilation in the gastric, superior mesenteric and inferior mesenteric arteries, while vasoconstriction was observed in the hepatic and splenic arteries.

The primary purpose of the present study was to explore the actions
of dopamine on the peripheral circulation of the endotoxin-shocked dog,
with a special emphasis on its possible effects in altering venous return
by obliterating intra- or extravascular pooling.

METHODS

Studies were carried out on forty-three adult mongrel dogs, unselected
by age or sex, weighing 7 to 15 kg. The first series was carried out in
twenty-five animals. They were anesthetized intravenously with sodium
pentobarbital (30 mg/kg). A venous return preparation was used as previously
described by Weil *et al.* (14) with modifications by Hinshaw *et al.* (5)
(Figure 1). A tracheotomy was performed and the animal was respired on
room air with a Starling constant volume respirator adjusted to 14 to 16
strokes/min and 300 to 400 ml/stroke. Systemic arterial pressure was
measured with a cannula inserted into the femoral artery, connected to a
Statham pressure transducer and monitored on a Sanborn direct writing
recorder. A median sternocotomy was performed. A reservoir system was
interposed between the central ends of the great veins and the right atrium
(the azygous vein ligated). The reservoir cylinder was kept between 35°
and 38° C. in a constant temperature water bath located approximately three
feet below the level of the dog. The system was primed with heparinized
blood from a donor dog. The flow was returned to the right atrium via a
Sigmamotor pump. The Sigmamotor pump speed was repeatedly adjusted until
the venous return remained constant. Venous return was measured periodi-
cally throughout this adjustment period with a graduated cylinder and
stopwatch. The level of the venous reservoir reflected changes in venous

return. A decrease in the level of the reservoir would indicate a decrease
in venous return, thus pooling of blood, either intravascular, extravascular,
or both. The atrial inflow was maintained constant for the duration of the
experiment (mean 75.7, 76.1 and 74.3 cc/min/kg for the control, endotoxin,
and dopamine treated groups, respectively). The level of the venous
reservoir was measured by the hydrostatic pressure of the column acting on
a pressure transducer connected io a Sanborn direct writing recorder.
Central venous pressure, the pressure at the orifices of the severed great
veins, was maintained at atmospheric pressure (0 mm Hg) by adjusting the
levels of the cannulas in the superior and inferior vena cavae so that
there were visually observed flutters in the vessels. Resistances were
calculated by dividing the mean systemic arterial pressure (mm Hg) by the
cardiac output (ml/min/kg). Experiments were divided into three groups.
The control group (five animals) received saline only at a constant infusion
rate (mean 0.764 cc/min) throughout the experiment. The endotoxin group
(10 animals) received a predetermined LD_{80} of E. coli endotoxin (1.2 mg/kg)
with a saline infusion (mean 0.879 cc/min) started 20 minutes prior to
endotoxin injection and maintained throughout the experiment. The third
group (10 animals) was similar to the endotoxin group but received dopamine
(California Biochemical Corporation, Los Angeles, California) instead of
saline. Dopamine (100 µg/cc) was dissolved in 0.9 percent saline and infused
(mean pre-endotoxin infusion = 0.840 cc/min) into the right atrium via a
Harvard infusion pump 20 minutes prior to endotoxin administration and
continued for 60 minutes post-endotoxin. Experiments were continued for an
additional 10 minutes after all infusions had been stopped. The rate of

infusion of dopamine varied with each preparation. The effects of the dopamine solution at various rates of infusion (0.4 to 2.0 cc/min) on venous return were determined and a control period was completed prior to endotoxin injection at the rate at which there was no change in venous return as indicated by the reservoir level. Following administration of endotoxin, the dopamine infusion rate was increased in order to prevent as much pooling as possible. After sixty minutes, the infusion was discontinued and the animal was observed for an additional ten minutes. This post-infusion period was added to determine if dopamine had a continuing vascular action.

Statistical evaluation was carried out by a modified student t-test. An evaluation of the difference between means equal to $p = 0.05$ indicated statistical significance.

An additional series of experiments was conducted on six dogs to determine the effects of post-treatment of endotoxin shock with dopamine. Experiments were carried out as above but additional catheters were placed in right and left atria, the pulmonary artery, pulmonary vein (via the left atrium) and the portal vein. These studies were designed primarily to study the cardio-pulmonary effects of endotoxin and dopamine. Ten minutes after intravenous endotoxin injection (1.5 mg/kg), dopamine infusion into the right atrium was begun at a low rate and gradually increased until the maximal rate of retrieval of blood into the venous reservoir was achieved. Dopamine infusion was terminated at forty minutes post-endotoxin and the animal was followed for an additional ten minutes.

A final series of survival experiments was carried out on twelve intact dogs, six of which received a similar regimen of dopamine as with the original

perfused animals. Dogs were anesthetized as above, but minimal surgical procedures were carried out. Mean systemic arterial pressure and central venous pressure were recorded for a two hour period after endotoxin in a treated group (six animals) which received dopamine infusion started ten minutes prior to endotoxin and continued for 60 minutes post-endotoxin. The untreated group (six animals) received a saline infusion instead of dopamine. The infusion rates were the same average rates as in the venous return experiments. Central venous pressure measured from a catheter advanced through the femoral vein with the tip positioned outside the right atrium provided an estimation of the degree of cardiac filling pressure on right heart failure. Hematocrits were obtained and pH of arterial and venous blood was recorded from samples taken from the above arterial and venous catheters. Survival rates of these animals were recorded during a period of forty-eight hours after endotoxin administration.

RESULTS

The rate of dopamine infusion into the right atrium was determined before the control period by starting at a low rate and gradually increasing the rate of infusion until the level of the venous reservoir was constant, i.e., the rate of dopamine infusion caused neither loss nor gain in volume of the reservoir blood (venous return equalled cardiac inflow).

Figure 2 illustrates the effects of increments of dopamine infusion on systemic arterial pressure, level of the blood in the venous reservoir, heart rate, pulse pressure and total peripheral resistance. At the lower dose range, averaging 7 µg/kg/min (0.764 cc/min), there was a tendency toward a decrease in mean systemic arterial pressure, reservoir volume,

heart rate and total peripheral resistance with very little effect on the magnitude of the pulse pressure. At the higher ranges, averaging between 17 and 34 µg/kg/min (1.91 to 3.82 cc/min) there were increases in all of the above parameters.

The effect of dopamine on venous return is illustrated in Figure 3. In the control experiments, on the average, there was a small decline in the level of the venous reservoir; i.e., there was slight pooling in the animal during the experiment. The endotoxin group pooled significantly and then began returning blood toward the latter part of the experiment. There was no significant pooling in the dopamine treated group until after the infusion was stopped at 60 minutes.

Figure 4 compares the amount of pooling in the three groups of animals. Mean values with standard errors and number of animals at each stage of the experiments are shown for each group. The group receiving endotoxin demonstrated the typical response to endotoxin: there was marked pooling which continued after the saline infusion was stopped at sixty minutes. In contrast, there was no significant pooling in the treated group until the dopamine infusion was stopped at sixty minutes. There was a significant difference (p<.05) in pooling between the endotoxin group at sixty minutes and the dopamine-treated group at sixty minutes and the dopamine-treated group at sixty minutes. After ten additional minutes, the pooling rate was not significantly different between treated and non-treated groups (p<.10).

Figure 5 illustrates the effect of dopamine on mean systemic arterial pressure. There was no significant difference (p<0.10) in mean systemic arterial pressure between any two groups at sixty minutes. The change in

total peripheral resistance in the dopamine-treated group was not significantly different (p<0.10) from the endotoxin group at sixty minutes (Figure 6).

Figure 7 illustrates the effect of dopamine infusion on heart rate after endotoxin injection. The mean heart rate for the dopamine-treated group was higher than the endotoxin group during the early post-endotoxin period and declined after the dopamine was stopped at sixty minutes. At seventy minutes, average changes in heart rate of the dopamine-treated group were significantly less than those of the endotoxin group (p<.01).

Table I illustrates the mean cardiopulmonary and peripheral vascular changes after endotoxin injection and dopamine infusion. In contrast to previous experiments, dopamine infusion was commenced ten minutes after endotoxin and continued for thirty minutes. Cardiac inflow was maintained constant during the course of the experiments. Results show that changes in portal vein pressure and cumulative pooling rates are directly correlated. Dopamine infusion resulted in a recovery of pooled blood in the animal and release to the reservoir which again was pooled rapidly in the animal ten minutes after cessation of dopamine infusion. Portal vein pressure was significantly less (p<0.05) after thirty minutes of dopamine infusion. Bradycardia ordinarily observed post-endotoxin was obviated with dopamine infusion and left atrial pressure was decreased in the presence of a steady cardiac inflow and relatively constant systemic resistance. Mean pulmonary artery pressure, pulmonary resistance and right atrial pressure remained at control levels or above, during dopamine infusion. Pulmonary vein pressure was low and relatively constant throughout the experiments. Pulmonary

resistance fell sharply following cessation of dopamine infusion.

Table II summarizes data from twelve intact non-perfused dogs pre-treated and infused with dopamine and utilized in endotoxin survival studies. Dopamine and endotoxin were administered at similar doses and periods as reported in the earlier venous return studies. Results suggest a survival benefit from dopamine since a greater percentage of treated animals survived (50% vs. 17%). Mean arterial pressure, central venous pressure, heart rate, and venous pH are relatively well maintained in the dopamine-infused animals. Increases in hematocrit are somewhat less on the average in the treated group although differences are statistically insignificant.

DISCUSSION

Results from these experiments show that dopamine infusion is very effective in preventing peripheral pooling that occurs after endotoxin. Its effectiveness is much more striking when administered as pre-treatment and continued during the post-endotoxin period. The hepatosplanchnic region appears to be the site of action of dopamine in preventing pooling, as reflected by changes in portal vein pressure. Other evidence in this regard is obtained from parallel experiments carried out in this laboratory showing that the weight of the isolated perfused liver and portal vein pressure are markedly reduced after endotoxin when dopamine is infused. In addition, pooling in the eviscerated dog given endotoxin is not altered by dopamine infusion in experiments utilizing a venous return preparation with constant cardiac inflow. Pooling caused by endotoxin may be extravascular as well as intravascular. Since dopamine reduced portal vein pressure, capillary pressure in the hepatosplanchnic region may be decreased thus

preventing loss of perfusate into the extravascular compartment. Hematocrit data in the present study were inconclusive, however, it is possible that dopamine may have reduced splenic volume thus increasing the numbers of circulating erythrocytes.

The primary purpose of the type of experimental preparation used in the current studies was to separate cardiac from peripheral effects during dopamine infusion. Preliminary clinical studies in shock patients (9) do not reveal the site of action of dopamine. Since it appears to exert a beneficial cardiac action (1,4,8,11,13), a problem arises in interpreting its mode of action in shock. The presently designed experiments appear to provide an answer to this dilemma. Although beneficial cardiac effects were strongly suggested in the current experiments (inotropic and chronotropic effects), dopamine clearly elicits a prominent action in endotoxin-shocked dogs by preventing the characteristic pooling described by others (10,14). If benefits were to accrue to the canine species from dopamine infusion after endotoxin, they might be expressed in terms of improved hemodynamic function and cardiovascular status. Circulating blood volume would be increased by restoration of perfusate from sequestered intravascular or extravascular regions by removal of venous constriction, as observed in the liver vasculature, which would effectively lower capillary pressure and obviate extravasation of perfusate as well as pooling in capillary and post-capillary regions. Although these findings are of a preliminary nature, they mark the first experimental demonstration of a beneficial action of dopamine by prevention of peripheral pooling and subsequent maintenance of cardiac output on the basis of a peripheral mechanism.

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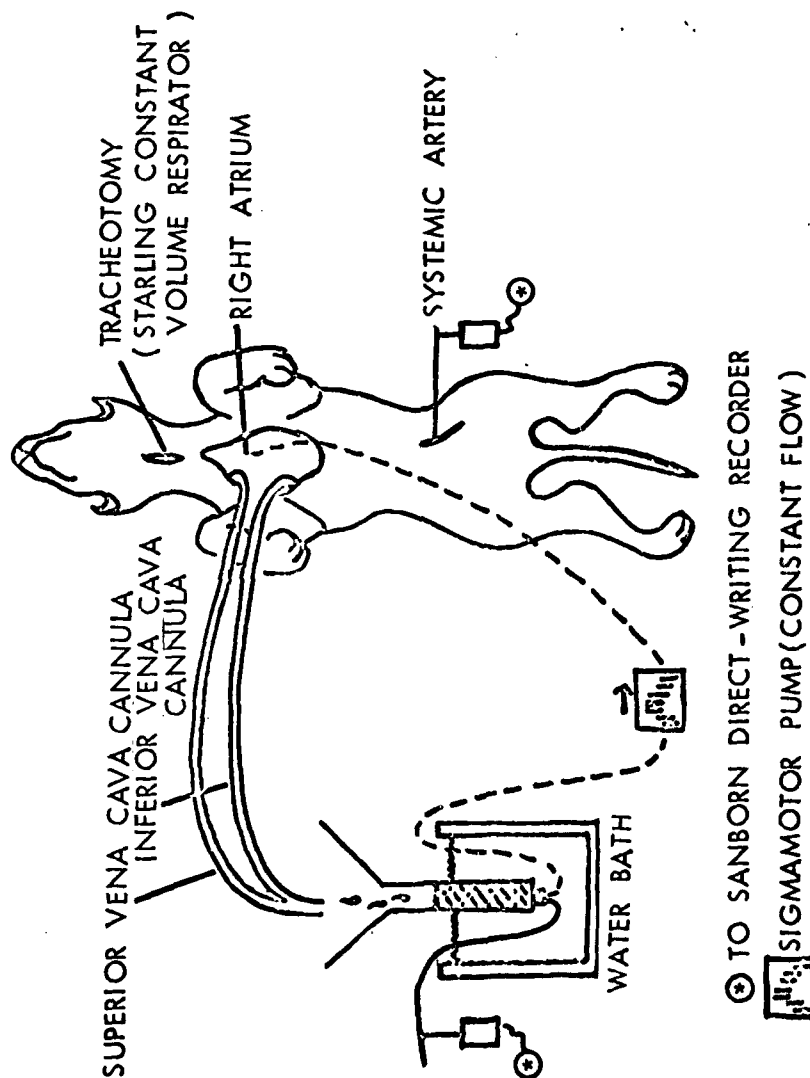
FIG.1 VENOUS RETURN PREPARATION

TRACHEOTOMY
(STARLING CONSTANT
VOLUME RESPIRATOR)

RIGHT ATRIUM

SYSTEMIC ARTERY

SUPERIOR VENA CAVA CANNULA
INFERIOR VENA CAVA
CANNULA

WATER BATH

⊛ TO SANBORN DIRECT-WRITING RECORDER

SIGMAMOTOR PUMP(CONSTANT FLOW)

Figure 1. Canine venous return preparation.

EFFECT OF VARIOUS RATES OF INFUSION OF DOPAMINE ON VENOUS RETURN AND HEMODYNAMICS.

SYSTEMIC ARTERIAL PRESSURE (mmHg)

VENOUS RESERVOIR (cc)

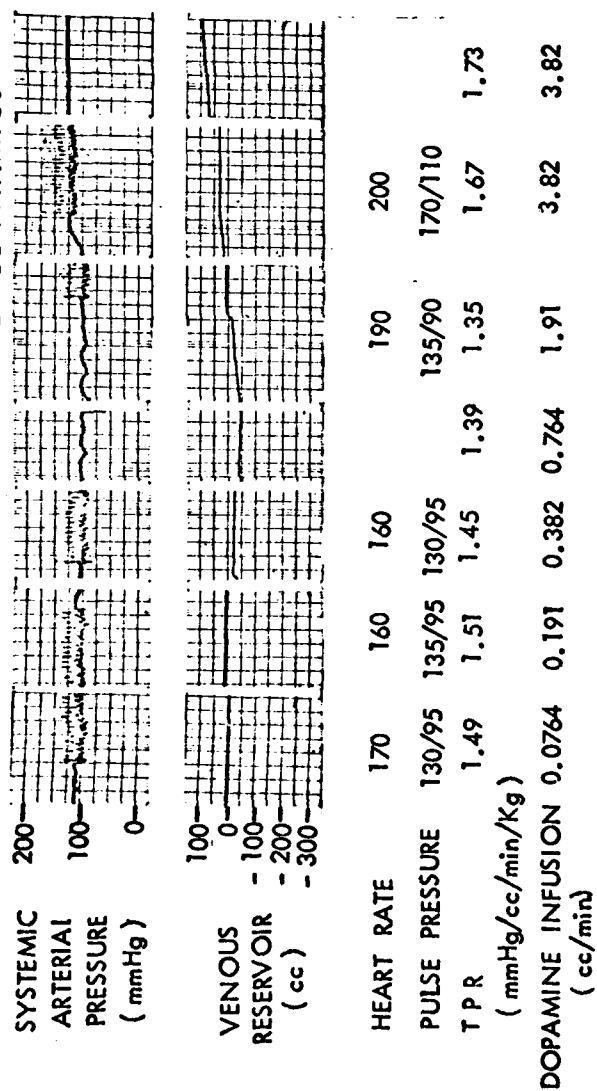| HEART RATE	170	160	160		190	200	
PULSE PRESSURE	130/95	135/95	130/95		135/90	170/110	
TPR (mmHg/cc/min/Kg)	1.49	1.51	1.45	1.39	1.35	1.67	1.73
DOPAMINE INFUSION (cc/min)	0.0764	0.191	0.382	0.764	1.91	3.82	3.82

Figure 2. Effect of various rates of infusion of dopamine on venous return and hemodynamics in the venous return preparation (representative record from a typical experiment).
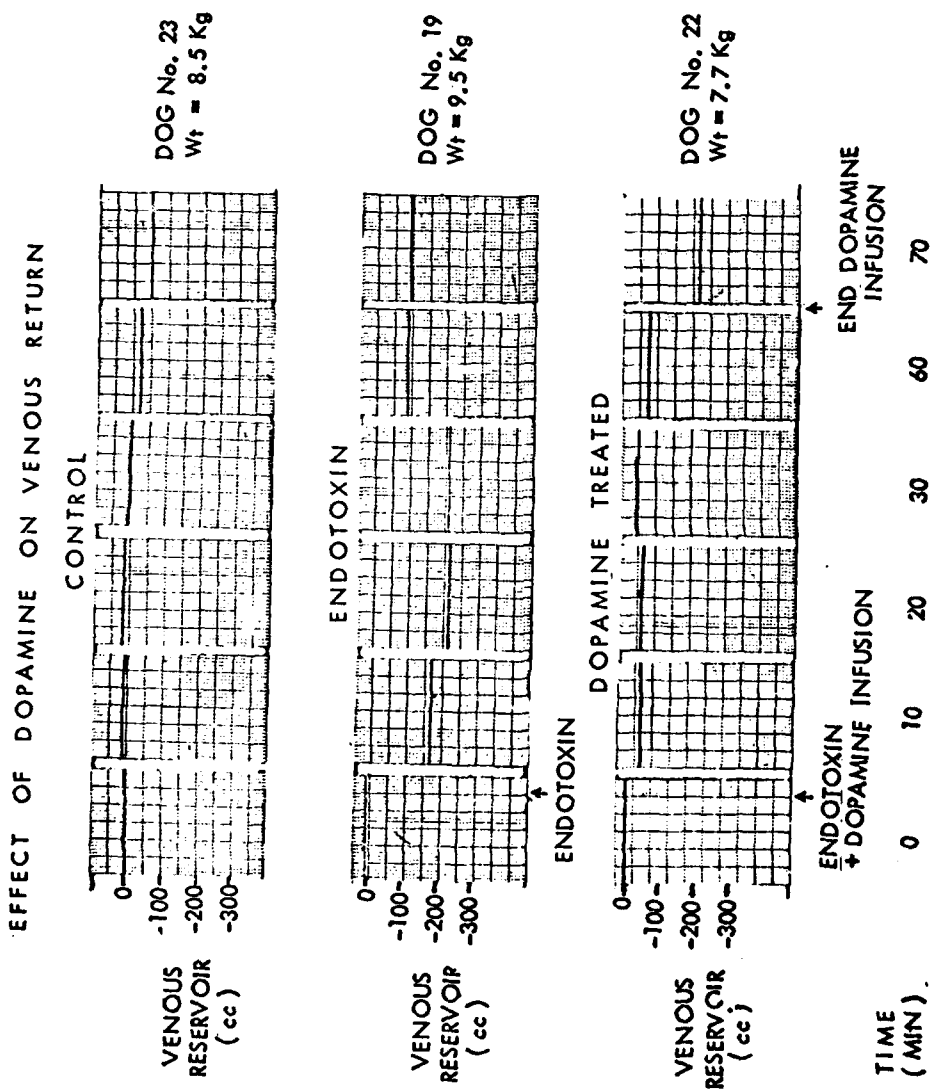
Figure 3. Effect of dopamine infusion on venous return after endotoxin in the venous return preparation (representative records from typical experiments in each group of animals).
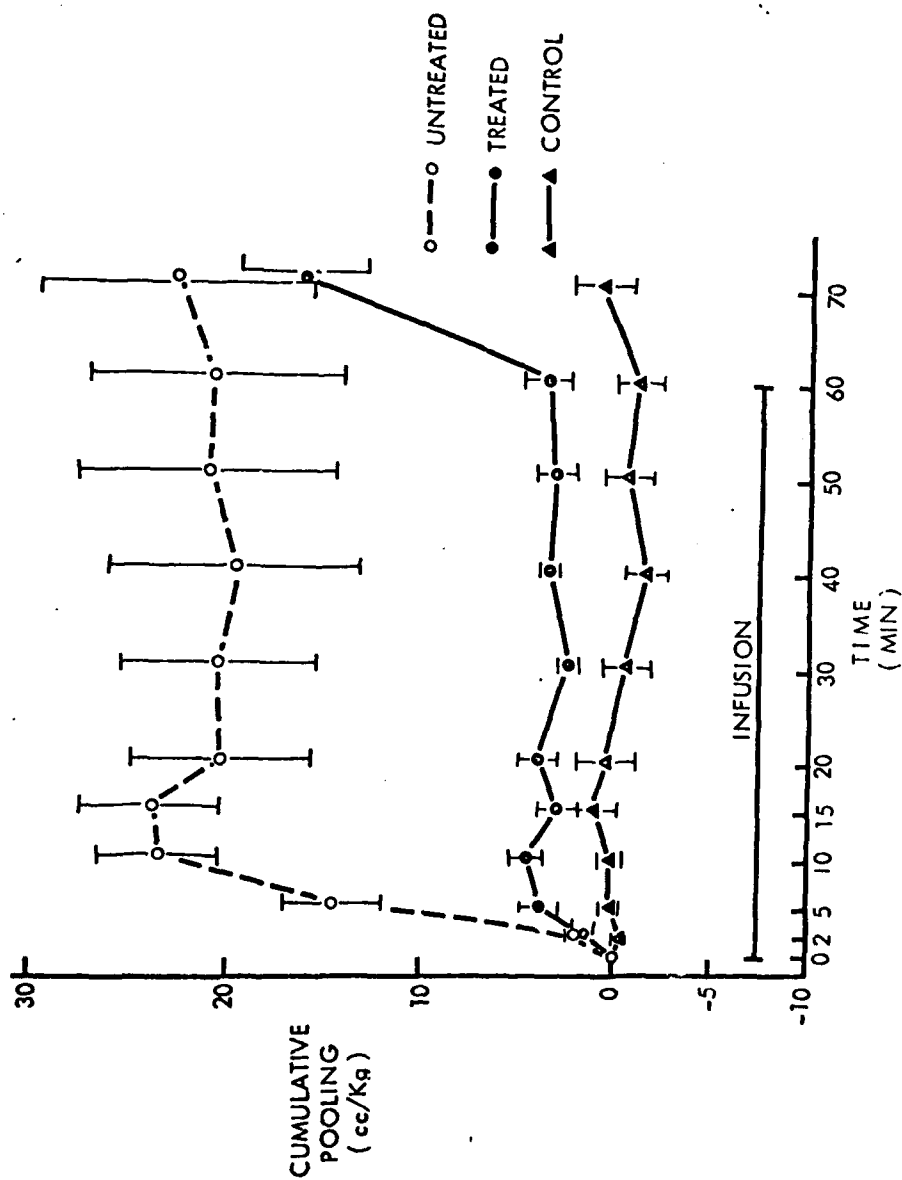
Figure 4. Effect of dopamine infusion on peripheral pooling. Each point represents

the mean ± S.E. for the number of animals shown at each point. Endotoxin: endotoxin,

LD_{80} with saline infusion; dopamine: dopamine infusion with endotoxin injection, LD_{80};
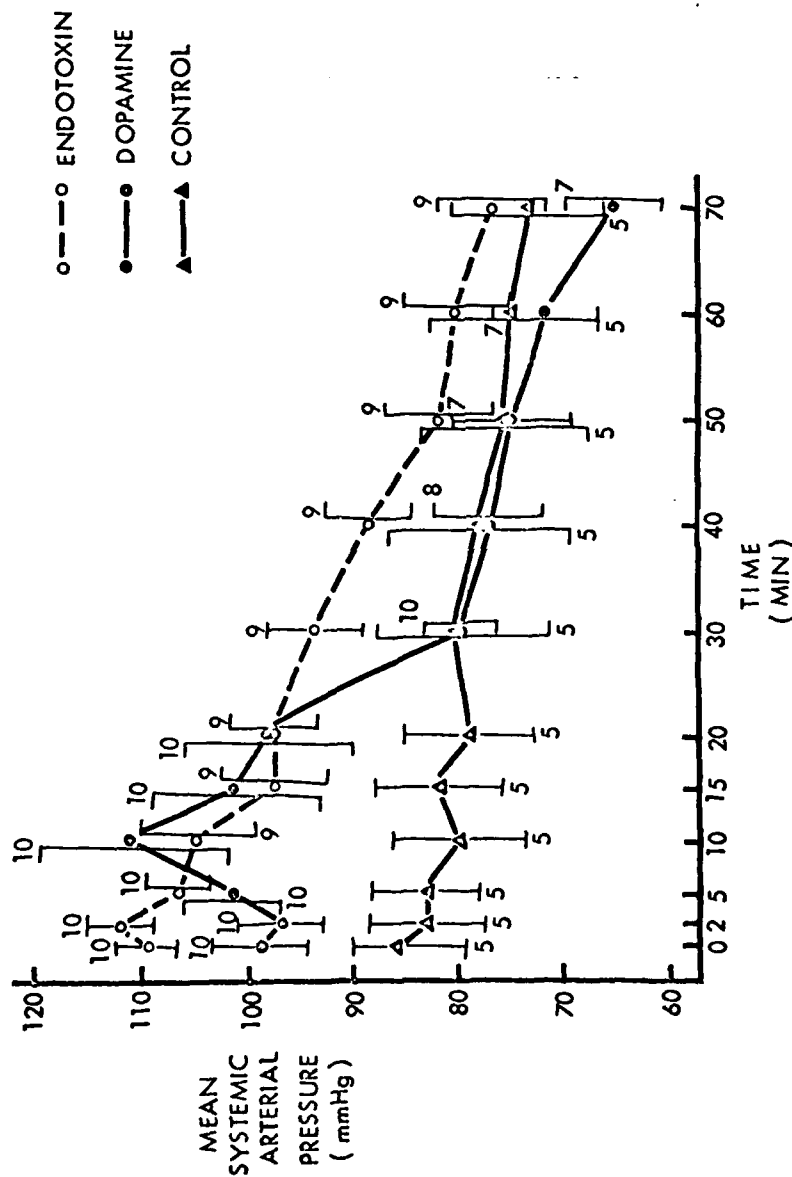
control: saline infusion only.

Figure 5. Effect of dopamine infusion on mean systemic arterial pressure. Each point represents the mean ± S.E. for the number of animals shown at each point. Endotoxin: endotoxin, LD$_{80}$, with saline infusion; dopamine: dopamine infusion with endotoxin injection, LD$_{80}$, control: saline infusion only.
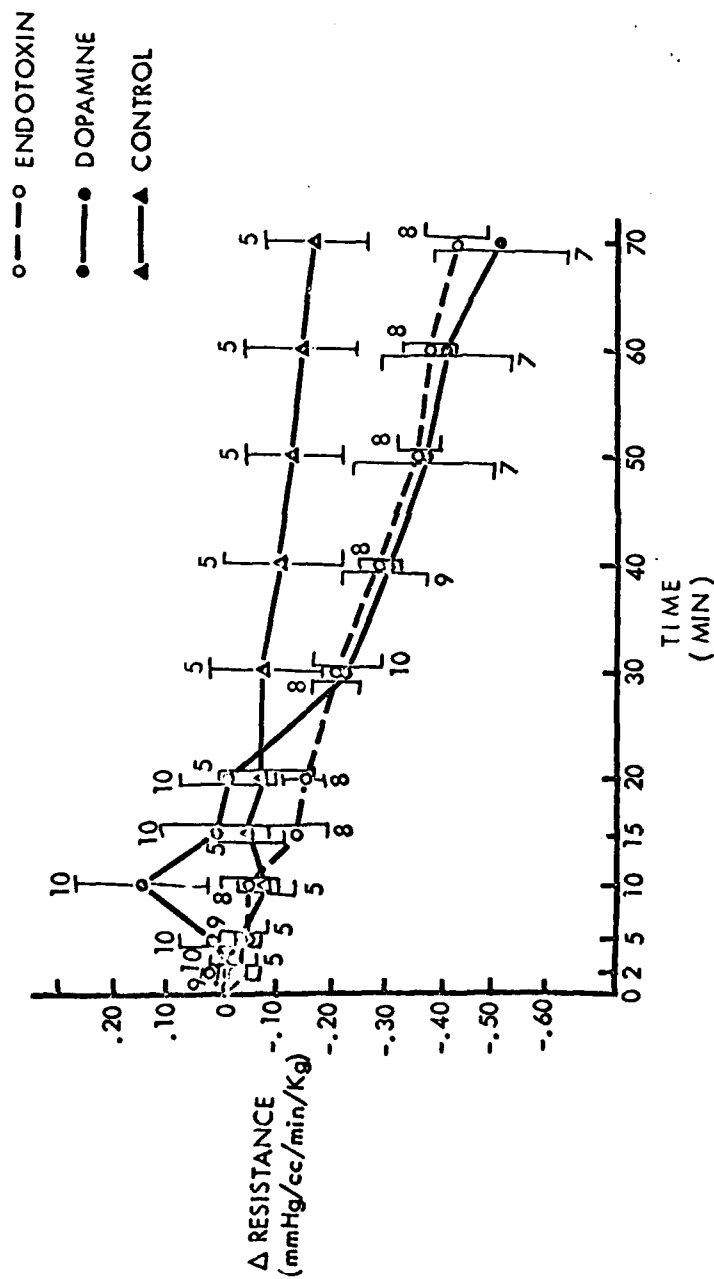
Figure 6. Effect of dopamine infusion on changes in total peripheral resistance.

Each point represents the mean ± S.E. for the number of animals shown at each point.

Endotoxin: endotoxin, LD_{80}, with saline infusion; dopamine: dopamine infusion with

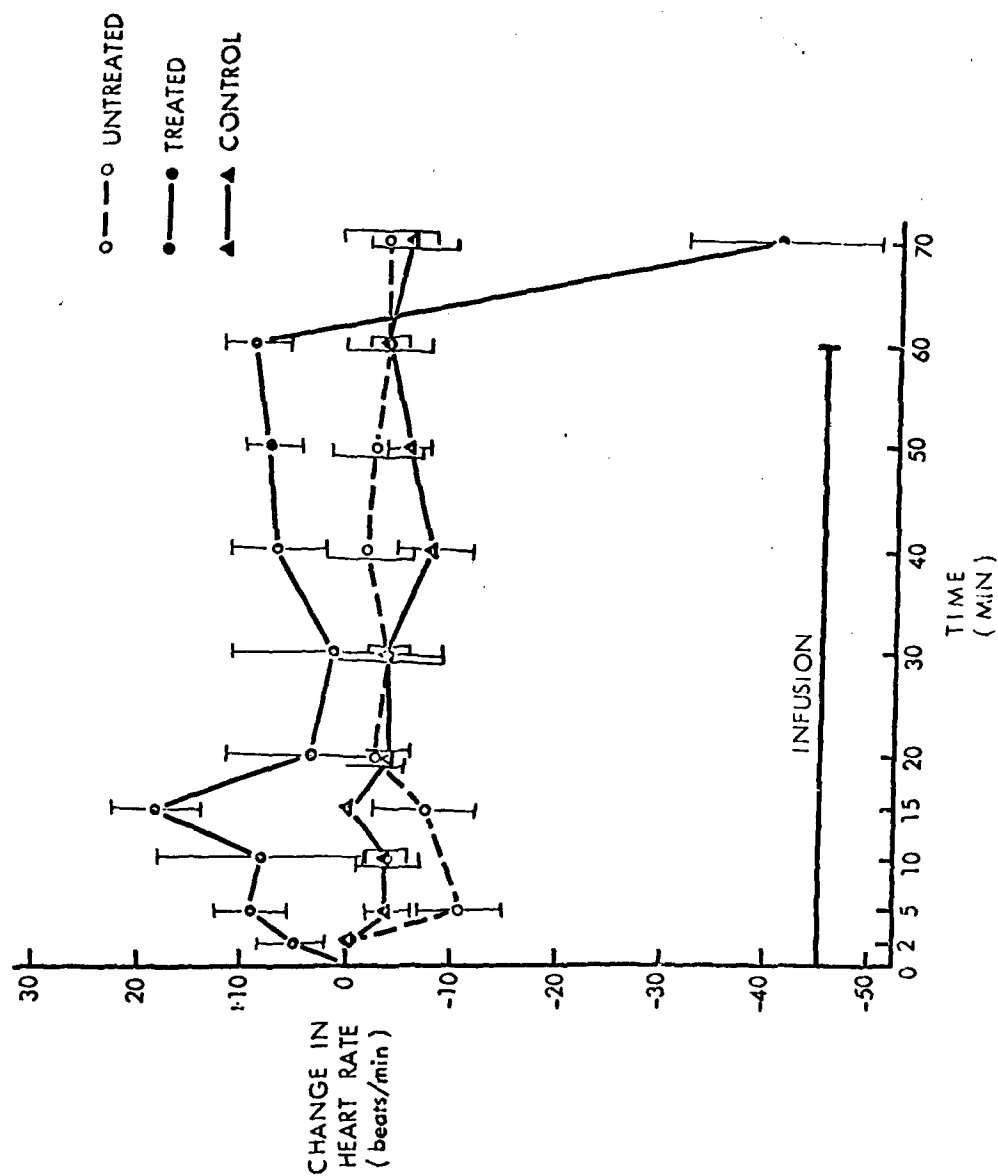endotoxin injection, LD_{80}; control: saline infusion only.

Figure 7. Effect of dopamine infusion on mean changes in heart rate. Each point represents the mean ± S.E. for the number of animals shown at each point. Endotoxin: endotoxin, LD_{80}, with saline infusion; dopamine: dopamine infusion with endotoxin injection, LD_{80}; control: saline infusion only.

TABLE I
CARDIOVASCULAR EFFECTS OF DOPAMINE IN ENDOTOXIN SHOCK
(POST-TREATMENT)
(Mean ± S.E.) (N = 6)

	0	+10	+20	+30	+40	+50
			Time (min)			
			Dopamine Infusion			
Portal Vein Pressure (mmHg)	10.3±1.7	18.1±3.3	14.9±1.3	14.6±1.1	10.0±1.2	12.8±1.3
Pooling (Cumulative) (cc/kg)	0	32.5±5.5	27.0±6.0	23.3±10.1	14.1±11.6	32.0±5.3
Systemic Resistance (mmHg/cc/min/kg)	1.5±.24	1.2±.17	1.4±.25	1.5±.23	1.4±.35	0.6±.08
Left Atrial Pressure (mmHg)	4.5±0.5	5.3±0.4	3.7±0.5	3.6±0.7	3.5±1.2	5.0±0
Heart Rate (beats/min)	122±11	115±10	170±9	174±25	142±26	157±3
Pulmonary Artery Pressure (mmHg)	13.8±1.5	21.6±2.7	17.3±2.9	17.9±3.4	12.8±3.4	17.6±4.4
Pulmonary Vein Pressure (mmHg)	7.3±1.4	7.1±1.5	6.4±1.9	6.7±1.3	5.0±2.1	6.5±1.4
Pulmonary Resistance (mmHg/cc/min/kg)	0.14±.03	0.24±.04	0.19±.05	0.23±.06	0.20±.11	0.10±.03
Right Atrial Pressure (mmHg)	3.3±0.4	3.1±0.6	6.1±3.4	7.3±4.6	8.8±5.6	7.6±3.7

TABLE II
EFFECT OF DOPAMINE* IN ENDOTOXIN SHOCK
(SURVIVAL STUDIES)**
(Mean ± S.E.)

	Time (min) Post-endotoxin								
	0	+10	+20	+30	+40	+50	+60	+90	+120
		Infusion Period							
Mean Systemic Arterial Pressure (mmHg)									
Untreated *	129±10	91±12	94±15	83±16	72±15	64±14	57±12	70±10	76±9
Treated *	143±7	135±12	130±4	125±3	126±4	117±10	97±14	53±7	64±12
Central Venous Pressure (mmHg)									
Untreated	2.4±0.8	1.1±0.8	0.5±0.3	0	0	0	0	0.6±0.6	0.4±0.2
Treated	2.4±0.7	1.0±0.5	1.4±0.7	1.3±0.6	1.5±0.8	1.1±0.9	1.4±0.8	2.1±0.8	2.3±0.7
Heart Rate (beats/min)									
Untreated	153±11	105±13	107±12	110±7	108±10	123±6	135±7	142±15	140±15
Treated	215±16	223±29	240±16	222±15	222±11	228±13	202±10	138±8	144±11
Hct									
Untreated	35±3	--	--	35±3	--	--	42±3	--	44±2
Treated	39±3	--	--	41±3	--	--	44±4	--	44±2
pH (arterial)									
Untreated	7.38±.01	--	--	7.30±.03	--	--	7.25±.06	--	7.33±.03
Treated	7.34±.05	--	--	7.28±.02	--	--	7.30±.01	--	7.33±.04
pH (venous)									
Untreated	7.36±.02	--	--	7.24±.05	--	--	7.18±.08	--	7.28±.04
Treated	7.28±.03	--	--	7.26±.02	--	--	7.26±.01	--	7.28±.04

*Untreated=Endotoxin with saline infusion (-10 to +60 min); Treated-Endotoxin with dopamine infusion (-10 to +60 min)

**Survival Rate: Untreated = 17% (N = 6); Treated = 50% (N=6)

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13. ABSTRACT

The present investigation was designed to evaluate the cardiovascular effects of dopamine (3-4 Dihydroxyphenylethylamine) in dogs administered endotoxin. In order to separate peripheral from cardiac effects, a venous return preparation was used in which cardiac inflow was held constant. Intra-arterial infusion rates of dopamine between 17 and 34 μg/kg/min caused increases in venous return and mean systemic arterial pressure. Dopamine markedly prevented pooling following an LD_{80} of endotoxin until infusion was stopped. Ten minutes after cessation of dopamine infusion, pooling rates were not significantly different from those of the untreated, shocked animals. Dopamine infusion begun ten minutes after endotoxin injection resulted in tachycardia and decreased left atrial pressure in the presence of a steady cardiac input and relatively constant systemic vascular resistance. Right atrial pressure and pulmonary vascular resistance were maintained above pre-endotoxin values during dopamine infusion, while portal vein pressure fell and venous return progressively increased. Results from survival studies in correlation with the above findings suggest beneficial actions of dopamine on both the left ventricle and peripheral vasculature in maintaining an adequate circulating blood volume.